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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,796	07/23/2001	Catherine Taylor	10799/13	2704

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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	14

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

F4

Office Action Summary	Application No.	Applicant(s)	
	09/909,796	TAYLOR ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,11,30,46,47 and 87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,11,30,46,47 and 87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's response filed May 30, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed November 6, 2002 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

2. Applicants amendment seeks to add claim 51. However, applicants original claim set contained a claim at that number that was canceled in applicants' communication mailed August 21, 2002. Because a newly added claim may not take the claim number of a canceled claim, the newly added claim has been renumbered as claim 87.

3. Applicants incorrectly state that claims 1, 11, 46, 47 and 51 are pending in the instant application. Claims 2, 3 and 30 have not been canceled by any amendment entered to date. Accordingly, claims 1-3, 11, 30, 46, 47 and 87 (re-numbered from claim 51 as described above) are pending in this case.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claims 1, 3, 11, 30, 46, and 47 and renumbered claim 87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of modulating apoptosis *in vitro* (both cells in cell culture and cell free assays) comprising the step of administering in vitro the agent putrescine and for methods of modulating apoptosis *in vivo* comprising the step of administering the agent spermadine, does not reasonably provide enablement for modulating apoptosis in any cell or in any mammal comprising the step of administering to the cell or mammal any agent that inhibits DHS-catalyzed eIF-5A activation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, and is repeated for the same reasons of record as set forth in the Office action mailed November 6, 2002.

Applicants have traversed the rejection above on the grounds that at first glance, the art cited by the examiner indeed supports the viewpoint that the role of polyamines in modulating apoptosis in cells is ambiguous, but that when studied further, the role of such polyamines is not ambiguous. Applicants have argued that the cited ambiguity arises from the fact that high levels of polyamines can be toxic via induction of apoptosis, while low levels of said polyamines can inhibit apoptosis, and that that *in vivo* work exemplified in the present application showing a delay in the onset of apoptosis in the the rat corpus luteum provides full enablement of applicants claims of *in vivo* use. In further support, applicants argue that polyamines have also been used to

prevent formation of an eIF-5A precursor *in vivo*, and that polyamines have been used to prevent senescence, a plant-version of apoptosis.

At the outset it is acknowledged that the specification provides sufficient support for the *in vitro* use of such a method on cells in culture, and for the *in vivo* use of spermadine in inhibiting apoptosis in rat corpus luteum. However, in contrast to applicants assertion, this showing does not provide enablement for the full scope of the claimed method. This is because the instant claims are much broader than the example provided in rat corpus luteum. Namely, applicants' claims seek to specifically encompass a method of modulating apoptosis using any agent that inhibits DHS-catalyzed eIF-5A formation in any cell, in any organism including humans, via any type of administration such that modulation of apoptosis is achieved. The *in vivo* exemplification in the rat corpus luteum does not support such breadth, particularly in view of the cited and acknowledged unpredictability.

Other than the rat corpus luteum, the specification provides no other exemplification of any whole animal model system, or any other agent used *in vivo* for that matter. While this does not necessarily preclude patentability, it is nevertheless strongly considered as a factor, particularly in cases where the art is considered unpredictable. See M.P.E.P. § 2164.03. As set forth via numerous citations in the previous Office action, the art of polyamine-mediated modulation of apoptosis, particularly that performed *in vivo*, is considered to be unpredictable. These citations clearly describe a dual effect of the use of polyamines. For example, Monti et al. (Life Sciences, Vol. 62, of record) teach that "in contrast to previous studies, exogenous polyamines failed to protect HL-60 cells against apoptosis caused by drib… depletion of

intracellular levels of putrescine and spermidine by (DMFO) delayed the onset of apoptosis by at least a day or so. Exogenous polyamines reversed the beneficial effect of DMFO and restored the apoptotic levels observed in dRib-treated cells. We suggested that polyamines, especially putrescine and spermidine, act as facilitating factors in the induction of apoptosis triggered by dRib in HL-60 cells." This teaching shows that in these cells, exogenous polyamines restored apoptosis, while depletion of endogenous polyamines delayed apoptosis, which stands in direct contrast to the broadly worded method of applicants instant claims that claim to use such compounds in the inhibition of apoptosis. Thus, as currently worded, applicants claimed method of administering an agent that is preferably a polyamine to inhibit the onset of apoptosis in any cell is considered to have unpredictable results.

Furthermore, applicants' response acknowledges such unpredictability. For example, applicants response states "The finding that exogenous polyamines both inhibit and promote apoptosis reflects the fact that, depending on the level applied, they can either inhibit the DHS reaction leading to the activation of Factor 5A and hence impede apoptosis, or induce apoptosis by reason of being toxic". Beyond the example provided in the rat corpus luteum, applicants have not demonstrated that they can overcome these acknowledged and cited problems to achieve inhibition of apoptosis in any cell or *in vivo* system.

Applicants have provided an in depth discussion of the mechanism of DHS-stimulated eIF-5A activation, wherein applicants argue that the instant isoform of eIF-5A is a legitimate target for modulating apoptosis because eIF-5A has been shown to regulate the expression of certain downstream apoptotic effector genes. From this mechanism, applicants assert that by

reducing the level of DHS, which activates eIF-5A, or by reducing eIF-5A itself, "one may then modulate the apoptotic pathways triggered by active apoptosis-induced eIF-5A." However, this example is strictly prophetic. In light of the cited and acknowledged unpredictability in the field, and given the breadth of applicants claims, one of ordinary skill in the art would necessarily have to resort to trial and error experimentation in order to practice the claims as broadly recited.

Newly added claim 87 is included in this rejection, because the active steps are identical to those set forth in claim 1. The limitations introduced in claim 87 are drawn solely to the catalytic events that occur during the performance of the actual steps set forth in claim 1, and do not comprise any different manipulative steps from those in said claim, and are thus not accorded patentable weight.

5. Claims 1 and 2 and newly renumbered claim 87 are rejected under 35 U.S.C. 102(b) as being anticipated by Tome et al. (Biochem J. 1997. 328:847-854), and is repeated for the same reasons of record as set forth in the Official action mailed November 6, 2002.

Applicants have traversed the rejection above on the grounds that the Tome reference teaches a different isoform of eIF-5A that controls cell division, as opposed the instant eIF-5A isoform that controls apoptosis.

Applicants arguments have been fully considered but are not convincing. Applicants' allegation that the eIF-5A isoform of Tome et al. is different than applicants instant eIF-5A

isoform is not convincing because applicants' argument is based on the allegation that the isoform of Tome et al. has a different function than the instant eIF-5A isoform. However, there is no evidence that these are actually different isoforms, because it is well known in the art that a polypeptide may have more than one function. Since they are both named eIF-5A, and because they are both sensitive to polyamine administration as acknowledged by applicant, there is strong evidence to presume that the isoforms are identical. Furthermore, applicants have provided no arguments pertaining to a structural difference between the two. Because applicants only cited argument that the isoform of Tome et al. is different from the instant isoform is that the eIF-5A of Tome performs a different function than the instant eIF-5A isoform, and because applicants have not provided any arguments or evidence that the isoforms differ in structure, and finally because it is well known in the art that one protein may perform multiple functions and impact multiple pathways, the eIF-5A of Tome is considered to be the same as that taught by applicant. Accordingly, the instant method drawn to inhibition of apoptosis via administration of a polyamine to a cell is considered to be inherent to the method of Tome et al. Support for this is drawn from M.P.E.P. § 2112.02:

> "...Under the principles of inherency, if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art device. When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process. In re King, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986)."

In the instant case, the prior art device of a polyamine, when administered to a cell to inhibit the formation of active eIF-5A as taught by Tome et al., is considered to inherently function to

perform the instantly claimed process of inhibiting apoptosis. Accordingly, the rejection is maintained.

Newly renumbered claim 87 is similar to claim 1 but seeks to add limitations drawn solely to events that occur naturally during the performance of the method steps that do not comprise any manipulative steps *per se*. Such limitations are not considered to carry patentable weight, because said events are considered to be inherent to the practice of the method steps. Therefore, claim 87 is included in the instant rejection for the same reasons of record.

6. Claims 1 and 2 stand rejected, and added claim 87 is newly rejected under 35 U.S.C. 102(b) as being anticipated by Tome et al. (Biol. Signals, 1997. 6:150-6) and is repeated for the same reasons of record as set forth in the Official action mailed November 6, 2002.

Applicants submit that the instant rejection is not valid for the same reasons as above, namely that the reference of Tome et al. teaches a different eIF-5A isoform than that of the instant claims. Applicants submit that the instant rejection should therefore be withdrawn.

Applicants arguments are identical to those considered above, and for the same reasons, are not considered convincing. The rejection is accordingly maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
August 11, 2003

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600